A systematic review of economic evaluations of conservative treatments for chronic lower extremity musculoskeletal complaints

Fenocchi, Linda; Riskowski, Jody L.; Mason, Helen; Hendry, Gordon J.

Published in:
Rheumatology Advances in Practice

DOI:
10.1093/rap/rky030

Publication date:
2018

Document Version
Author accepted manuscript

A systematic review of economic evaluations of conservative treatments for chronic lower extremity musculoskeletal complaints

Linda Fenocchi[1,2], Jody L Riskowski[1], Helen Mason[2], Gordon J Hendry[1]

[1]Glasgow Caledonian University, School of Health and Life Sciences, Glasgow, UK
[2]Glasgow Caledonian University, Yunus Centre for Social Business & Health, Glasgow, UK

Correspondence to: Linda Fenocchi, Glasgow Caledonian University, School of Health and Life Sciences / Yunus Centre for Social Business & Health, M201 George Moore Building, Cowcaddens Road, Glasgow, UK , G4 0BA. E-mail: linda.fenocchi@gcu.ac.uk

Abstract

Objective. To appraise and synthesise studies evaluating the clinical and cost effectiveness of conservative interventions for chronic lower extremity musculoskeletal (MSK) conditions and describe their characteristics, including type of economic evaluation, primary outcomes and which conditions.

Methods. The search strategy related to economic evaluations of lower limb MSK conditions that utilised conservative therapies. Eight electronic databases were searched (CENTRAL, MEDLINE, PubMed, EMBASE, CINAHL, PEDro, NHSEED, and Proquest) and reference lists from included articles. Quality of articles was appraised using a modified

version of the economic evaluations' reporting checklist (economic) and The Cochrane Collaboration's tool for assessing risk of bias (clinical).

Results. Twenty six studies were eligible and included in the review. Economic evaluations of conservative interventions for osteoarthritis or pain affecting the knee/hip (N=25; 93%) were most common. The main approaches adopted were cost utility analysis (N=17; 68%) or cost effectiveness analysis (N=5; 19%). Two studies involved interventions including footwear/foot orthoses; for heel pain (N=1; 4%) and overuse injuries (N=1; 4%). 50% of economic evaluations adopted the EQ-5D-3L as the primary outcome measure for quality of life and QALY calculations.

Conclusions. Economic evaluations have been conducted largely for exercise based interventions for MSK conditions of the hip and knee. Few economic evaluations have been conducted for other clinically important lower limb MSK conditions. A matrix presentation of costs mapped with outcomes indicated increasing costs with either no difference or improvements in clinical effectiveness. The majority of economic evaluations were of good reporting quality, as were the accompanying clinical studies.

Key words: systematic review, economic evaluation, lower extremity musculoskeletal conditions, cost effectiveness, conservative interventions

Key messages

- Comprehensive systematic review of economic evaluations of conservative treatments for common lower extremity musculoskeletal conditions.

- Economic evaluations of hip and knee osteoarthritis dominate cost-effectiveness literature for lower extremity musculoskeletal conditions.
- Reporting quality of clinical and economic evidence for lower extremity musculoskeletal conditions is generally good.

INTRODUCTION

Worldwide over 20% of the population have a musculoskeletal (MSK) condition (1). These conditions are one of the main drivers of increasing years lived with disability (YLD) (2, 3) and their management has major implications for health care resource use. A wide range of inflammatory and degenerative conditions are classed as MSK conditions (4) and they are often characterised by pain, limitations on physical function and reductions in health-related quality of life (5). For many MSK conditions the first line of management is conservative treatment. This may include options such as exercise programmes, self-management education, and physical therapies (6). However, evidence of clinical and cost effectiveness for conservative interventions for MSK conditions remains equivocal. While there is a growing evidence base for clinical effectiveness for some conservative treatments, the evidence for cost effectiveness is often lacking. This is problematic given that health care systems must deal with resource allocation constraints. To maximise health using the resources available it is necessary to make choices between competing claims.

The overall aim of economic evaluations in health care is to aid decision makers to make efficient and equitable decisions (7). Economic evaluation involves the comparison of two or more health care interventions, typically comparing a new intervention with usual care, in terms of the costs and the consequences (7, 8) The inclusion of the outcomes as well as costs is crucial if we are to determine which interventions produce the greatest health gain for our given budget. (For a glossary of economic terms, see (9))

Systematic reviews are useful to assess evidence of effects, adverse effects and health-related quality of life (HRQOL) as well as to identify gaps in research (10). Systematic reviews of economic evaluations can be used to establish the current state-of-the-art in economic evaluations of interventions that assess cost effectiveness and provide a foundation for higher methodological standards (8, 11). While previous reviews of cost-effectiveness of non-pharmacologic and non-surgical treatments for MSK conditions have focused on specific patients or interventions (12, 13), the current study sought to increase scope to include any attempt to compare costs with benefits for any lower extremity MSK condition.

Accordingly, the aim of this review was to: identify and critically appraise the current evidence of clinical and cost effectiveness of conservative interventions for the treatment of lower extremity MSK conditions to determine whether there is sufficient evidence to inform policy and practice (14); and identify and describe the characteristics of these

economic evaluations including type of economic evaluation, primary outcomes, which lower extremity MSK conditions, and a synthesis of their results.

METHODS

Protocol

The protocol for the systematic review was submitted and approved *a priori* (PROSPERO 2015:CRD42015024441 (15)) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16).

Search strategy

Peer-reviewed literature was searched using a predefined strategy using a combination of medical subject headings (MeSH) related to MSK and physical body location and keywords (any field), including text words related to economic evaluation (supplementary table S1, available at *Rheumatology Advances in Practice* online). The strategy was wide in scope in order to be inclusive so that relevant studies were returned.

The search was conducted for studies published up to10 September 2017. Eight databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE), PubMed, Excerpta Medica database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro), NHS Economic Evaluation Database (NHS

EED)(addition of bibliographic records to NHS EED ceased after 31 March 2015), and Proquest. Results were imported to Endnote (Endnote; Version 7.1, Thomson Reuters).

Inclusion Criteria

Articles reporting an economic evaluation of health professional delivered conservative intervention for the treatment of MSK conditions of the lower extremities were the focus of the systematic review (Table 1). Medical treatments such as pharmacological, homeopathic and surgical interventions were excluded. Studies that were primarily clinical but had some analysis of cost in relation to benefit (using an economic tool or method to calculate outcome) were included prior to a process of screening to ascertain whether they met economic evaluation definitions (UK classification system (7)). Articles reporting embedded economic evaluations, including randomised controlled trials or quasi-randomised controlled trails, controlled trials, pilot studies were eligible for inclusion. Adult lower extremity MSK conditions considered theoretically to have a mechanical aetiology (such as osteoarthritis (OA), stress trauma, overuse injuries, or biomechanical misalignment) were included. In addition, only conditions affecting the lower limb (International Classification of Functioning, Disability and Health (17) structures of the lower extremity, s750; hip, s75001; thigh, s7500; knee, s75011; ankle and foot, s7502) were considered.

Exclusion Criteria

Pharmacological, and homeopathic, or surgical interventions were excluded. Systemic conditions, such as diabetes or rheumatoid arthritis, as well as neurological conditions whereby the primary condition was not MSK in origin, were excluded. Lower extremity MSK conditions resulting from acute or injury trauma (e.g., athletic ankle sprain, professional ballet injuries) were excluded. MSK complaints in axial regions, torso and upper extremity were excluded. Non-peer reviewed documentation, such as commentaries, letter, editorials, were excluded. Articles were limited to those available in English. No restrictions were placed on publication date.

Study selection

Studies were identified, selected and appraised using methodology in line with The Cochrane Handbook for Systematic Reviews (10). Title screening of studies was undertaken by one reviewer [LF], using the keywords and MeSH terms to determine if the title warranted further consideration for review. This was followed by independent review of abstracts, then full text, by two authors [LF + GH]. At each stage, reviewer agreement or disagreement was recorded with justification. For included articles, if the economic evaluation referred to a primary clinical paper then a copy of that was sought and included in the review. Economic and accompanying clinical articles were treated as one study. Reference lists of included studies were hand searched.

Data extraction

The data extraction tool for this review included patient population, study design, economic evaluation method, intervention, follow-up, and clinical and cost effectiveness outcomes. This data extraction tool was used independently by two authors [LF and GH].

Quality assessment

Reporting quality of economic evaluations of the included studies was independently assessed by two authors [LF and GH] using a modified version of the economic evaluations' reporting checklist (18, 19). The modified checklist included 13 items (plus an additional 2 items applicable for decision analytic modelling studies). The included items were selected based on their direct relevance to economic evaluations of single clinical treatment studies and the specific research question for the systematic review. Clinical studies were evaluated for their quality separately using The Cochrane Collaboration's tool for assessing risk of bias (10, 20) .

Synthesis of evidence

Evidence of cost-effectiveness relative to clinical effectiveness was summarised using a matrix (8). The matrix was developed to aid discussion about the choices between health care interventions that are available to managers and clinicians. It provides a visual representation and summary of available clinical and economic evidence. By mapping these two sources of evidence together it demonstrates both technical efficiency (which interventions are offering most clinical benefit for the resources used) and opportunity cost considerations (what the next best option would have offered) at the same time.

Statements of clinical effectiveness and evidence of cost-effectiveness was accepted as reported by study authors. This was a pragmatic decision based on the fact all included studies had been peer reviewed. Clinical effectiveness relative to the treatment comparator is mapped horizontally. Evidence of impact on resources in terms of marginal change is mapped vertically. The main feature of utility of the matrix is that it provides easily accessible information to aid decision-making by healthcare providers concerning treatment options.

It is recommended that only studies appraised as good quality are mapped in the matrix (8). Studies were included in the matrix if they had a quality score between 70% to 100% for both clinical reporting (10, 20) and economic reporting (18, 19). Reported conclusions about clinical and cost effectiveness were mapped to one another. For studies that involved more than one intervention-comparator pairing, these were mapped by each individual intervention to the comparator (thirteen studies, 21 pairs). Studies with insufficient information about intervention-comparator pairings could not be mapped (thirteen studies).

RESULTS

Search results

A total of 24,754 records were returned as a result of searching, and after removing duplicates there were 18,852 records (Figure 1). Based on the inclusion and exclusion

criteria, the review of titles excluded 17,274 records, leaving 1,578. At the abstract stage, 1,492 were excluded, leaving 86 records for full text review. 27 articles met the inclusion criteria including one additional article identified through reference lists. Of these, two economic papers (21, 22) reported on the same analysis of the same study, meaning in total there were 27 articles representing 26 unique studies.

Studies included in review

Data extracted from 26 included studies were from the economic articles (21-47) and their associated clinical papers (48-64) (Table 2). The majority of studies were written as separate economic evaluations (N=15; 58%) with an associated clinical paper, while a minority included embedded reporting of economic evaluation (N=11; 42%) in the parent article. Using the UK definition of economic evaluation approaches (7), there were: 17 cost utility analyses (CUA), five cost effectiveness analyses (CEA), three cost consequence analyses (CCA), and one cost minimisation analysis (CMA). Articles were published between 1999 and 2017.

Conservative interventions

The conservative interventions of the included economic evaluations were of exercise-based intervention (N=11; 42%), education (N=3; 12%), combined exercise and education (N=3; 12%), combined exercise and diet (N=2; 8%), acupuncture (N=3; 12%), footwear/orthoses (N=2; 8%), physical therapy (N=1; 4%) and mud-bath therapy (N=1; 4%). Studies were largely focused on interventions involving an exercise component for

OA or pain management affecting the knee/hip (N=24; 92%). The remaining studies evaluated conservative interventions for heel pain (N=1; 4%) and lower limb overuse injuries (N=1; 4%).

Primary outcome measures

Of the included studies, the most commonly used outcomes measures adopted for evaluating the clinical and cost-effectiveness of conservative treatments were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (cost-effectiveness analysis) and the generic preference based measure EQ-5D-3L, developed by the EuroQoL group (cost-utility analysis). Two studies were concerned with foot and ankle conditions, using the Foot Health Status Questionnaire (FHSQ) (38) and an investigator-developed questionnaire (43) respectively.

Five generic preference based outcome measures were used by 21 economic evaluations: EQ-5D-3L (12 CUAs, 1 CEA and 1 CCA), SF-36 (2 CUAs, 1 CEA [RAND-36], 1 CMA), SF-12v2 (1 [SF-6D]) CUA), AQoL-6D (1 CUA), and HUI-3 (1 CUA). Each of these tools produce utility values that can be used in the calculation of QALYs (quality adjusted life years), essential for comparisons across different diseases. Three studies collected only clinical measures of health for hip OA and knee OA and so were restricted to CEA methodology (i.e. cost per unit of improvement in condition-specific outcome measures) (27, 42, 47). One study used

an investigator-developed questionnaire to undertake a CEA (39). Two studies collected utilisation of health care and cost data and conducted a CCA (34, 43).

Quality of the evidence

The reporting quality of economic evaluations and related clinical studies was generally good (for this review, defined as scoring between 70% to 100% for items on each reporting quality checklist) (Table 3). Ten studies reported on all 13 of the economic evaluations' reporting list items that were selected for appraisal (21, 22, 24, 27, 28, 31, 33, 35, 36, 41, 44). A further nine studies reported on more than 70% of the items (23, 25, 26, 32, 37, 42, 46, 47, 65) and four studies were considered to have reported on at least half of the key elements (29, 34, 39, 43). The remaining three were appraised to have poor reporting quality (30, 40, 45). Witt et al (45) did not report adequately on resource use and methods for estimation of quantities and unit costs. Juhakoski et al (30) reporting of methods for estimation and quantities of costs was restricted because they were using study data collected for clinical effectiveness considerations, not economic. Stan et al (40) was judged to have poor reporting quality for both clinical and economic considerations. Sampling strategy was not reported, nor why EQ-5D-3L administration was at different follow-up intervals for different intervention arms.

Sixteen clinical studies were appraised as good quality with low risk of bias (21, 24, 25, 27, 30, 43, 46, 48, 49, 51-53, 55, 59-61), five appraised as medium risk of bias (29, 38, 41, 57, 58, 62), and four as high risk of bias (37, 40, 50, 54). Blinding and attrition risks were

common to most of the studies. As would be expected with interventions involving such treatment as exercise or footwear, it was not possible to blind participants and assessors. Higher risk of bias due to incomplete outcome data was also noted in more than half of the studies (21-23, 25, 29-31, 33, 37, 39, 40, 42, 44, 45, 50-52, 54, 60, 65) although this is not unusual for interventions that require adherence, such as exercise therapies. It should be noted that Tan (41) reported that a clinical article is forthcoming, and so the judgement about risk of bias, made on the basis of the available evidence in the economic evaluation article.

Cost effectiveness of interventions

Economic evidence, for studies with a quality score between 70% to 100% for both clinical reporting (10, 20) and economic reporting (18, 19) (Table 4), was synthesised in a matrix (Table 5). The reported evidence for exercise interventions for hip/knee OA is mixed, with studies reporting in A1 (evidence of greater clinical effectiveness and reductions in costs) (25, 28, 42, 46), B1 (evidence of greater clinical effectiveness with no difference in costs) (24, 28) and B2 (evidence of no difference in clinical effectiveness and no difference in costs reported, relative to comparator) (21, 22, 26, 44), C1 (evidence of greater clinical effectiveness and greater costs) (36, 44) and C2 (evidence of no difference in clinical effectiveness and greater costs) (28, 35, 66) and C3 (evidence of less effectiveness and greater costs) (24). Acupuncture mapped in C1 (44); indicating greater clinical

effectiveness with greater cost, when compared to exercise and advice. However, the same study sought to compare true and non-penetrating acupuncture and found no difference in clinical effectiveness and no difference in costs (mapping in B2). Mud-based therapy for pain management in knee OA (46) mapped in A1, reflecting the research findings that clinical effectiveness of standardised care was enhanced by the addition of MBT to standardised care.

DISCUSSION

The findings of this review provide an overview of the characteristics and reporting quality of economic evaluation of conservative interventions for common lower extremity MSK conditions. Twenty-six unique studies which assessed clinical effectiveness and cost effectiveness of conservative, non-pharmacological and non-surgical rehabilitative interventions for lower limb musculoskeletal conditions were identified and appraised. Despite a deliberately broad scope search strategy, it is of note that the overwhelming majority evaluated treatments for hip OA and knee OA involving an exercise component, with only 2 focused on common disorders of the foot and ankle, and 1 on chronic pain (with OA of the hip or knee included in the range of conditions). This is unsurprising given the prevalence of hip/knee OA problems in populations (67) and the medical priority to slow disease progression towards knee and hip replacements at end-stage disease.

Reporting quality for economic evaluation was generally in accordance with clinical reporting quality recommendations, whether published as a separate economic evaluation article or within the clinical article, with a few exceptions. Of those that were judged to be less well reported for economic evaluation than for clinical effectiveness, this may have been a consequence of the scale of the research programme and study objectives. Pilot and feasibility studies are typically conducted with smaller samples, and objectives are inherently different to that of definitive RCTs. Others faced restrictions on the type and scope of economic analysis that can be conducted when data has not been explicitly collected for economic evaluation as part of the original study design. This was the case for Juhakoski et al (30) who conducted a post-hoc economic evaluation using information collected during the clinical study. In addition, consideration should be given to whether weaker reporting quality may also partly be a consequence of translation (for example, when an article has a dual language abstract (40)).

To make decisions about resources it is useful to present information on costs and outcomes for each of individual intervention arm with the comparator. For example, Barton et al (23) involved multiple trial intervention arms: usual care provision compared to dietary intervention, to strengthening exercises, and to a combination of diet and exercise. The use of a comparator that is equivalent to standard (or usual) care provides a pragmatic result that can be used for making policy decisions about resource allocation. However, when studies involve more than one intervention and a comparator that is not

usual care, the external validity of both the RCT and the economic evaluation become limited.

The outcome measures adopted by included studies were largely appropriate for the evaluations of interventions' clinical and cost-effectiveness. Provided that sufficient validation and evaluation of measurement properties have been undertaken patient reported outcome measures provide a means by which to assess and quantify the health consequences of health care for patients with specific conditions. In contrast economic evaluation requires comparability across different disease conditions via use of a common metric. QALYs provide a common metric and can be calculated using preference-based single index measure for health. These can be collected using generic preference based measures such as EQ-5D (used by the majority of included studies) and also by conversion to SF-6D from SF-36 and SF-12. However, the measurement properties of the generic preference based measure (i.e. EQ-5D) for specific conditions should be known/evaluated prior to use in that specific clinical context. The lack of specificity of generic preference based measures has been highlighted as a concern (68). Given the potentially small and subtle changes that occur following conservative interventions for MSK conditions, accurate estimation of improvements is important to estimate both the burden and the consequent impact of health care treatments. The possibility of ceiling effects limiting sensitivity to small changes in health has led to the development of a new 5 level version of EQ-5D. EQ-5D-5LThis may prove more useful for health outcomes research in a

musculoskeletal population in future due to the ability to better discriminate between full health states, particularly for domains such as mobility (69). Research to understand the full implication of using EQ-5D-5L and its value sets for QALY calculations is supported by NICE (70).

The paucity of evidence about cost effectiveness of conservative, non-pharmacological and non-surgical rehabilitative interventions for the range of lower limb MSK conditions is a concern. Consistent pressures on demand for health care worldwide, coupled with a changing landscape due to demographic and health care developments, make the need for clinical and cost effectiveness evidence more pertinent. Including economic evaluation in clinical trial design will build the evidence base about clinical and cost effectiveness. Presenting the evidence in a form such as the matrix used for this review aids decision makers to consider clinical and economic evidence together. The ideal intervention would be in A1 where it would be both more effective and use less resources, but C1 is typically where new treatments map. Often a new intervention offers improvements in outcomes but generally will also cost more (i.e. increased resource use). The studies included in this review mainly fall into C1 and C2. Presentation of clinical and cost effectiveness information in a matrix is intended to facilitate discussions about ways to achieve maximum health gain through resource allocation decisions. C1 indicates greater costs with greater effectiveness. To make use of this, decision makers should also consider specific health care system implications (for costs) at their local system level, and country

specific cost-effectiveness thresholds (explicit or implicit). C2 costs more and does not deliver outcomes any better than the comparator (in the trial), so it would be advisable not to introduce this intervention.

The systematic review sought to be broad in scope to encompass any type of economic evaluation of any conservative intervention for any lower extremity MSK condition of mechanical aetiology. To focus on a specific disease and a specific physical location using a PICO type strategy would have narrowed the returned titles but at the cost of restricting confidence that all relevant studies had been identified. There are limitations to this systematic review that are worth highlighting. Restricting studies to conservative treatments excluded co-provision of treatments (for example, exercise therapy with pharmacological treatment). This was purposeful in order to determine the reported clinical effectiveness of conservative treatment. It may be that co-provision of treatment would be more aligned to real world health care practice and should be considered. The desire to consider clinical effectiveness meant excluding economic evaluations of interventions undertaken in general populations. Research of this nature is often focused on preventative measures and the economic interest is prediction of prevented demand and avoided costs, rather than management of existing health care budgets given current demand for health care.

The dominance of exercise based interventions for MSK conditions of the hip and knee, with few economic evaluations of other clinically important lower extremity conditions,

such as foot and ankle disorders, highlights a gap in the literature and therefore current knowledge. Common MSK conditions of the lower leg, such as Achilles tendinopathy or plantar fasciitis, are prevalent (71-73) and have resource implications for health care systems. It would appear that the body of clinical evidence for conservative interventions for conditions such as these (74, 75) is not currently complemented by economic evidence, although the reasons for this are unclear.

Acknowledgements
This systematic review was undertaken as part of a PhD at Glasgow Caledonian University; studentship 2014SHLS024S.
Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.
Disclosure statement: The authors have declared no conflicts of interest.

References

1. March L, Smith EU, Hoy DG, Cross MJ, Sanchez-Riera L, Blyth F, et al. Burden of disability due to musculoskeletal (MSK) disorders. Best Pract Res Clin Rheumatol. 2014;28(3):353-66.
2. Woolf AD, Erwin J, March L. The need to address the burden of musculoskeletal conditions. Best Pract Res Clin Rheumatol. 2012;26(2):183-224.
3. Vos Tea. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(December 15/22/29):34.
4. ICD-10-CM Official Guidelines for Coding and Reporting. 2014.
5. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. 2003.
6. NICE. NICE Pathways. Musculoskeletal conditions overview. 2014.
7. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford University Press; 2015.
8. Donaldson C, Mugford M, Vale L. Evidence-based Health Economics: From effectiveness to efficiency in systematic review. 1 ed: BMJ Books; 2002. 168 p.

9. Shiell A, Donaldson C, Mitton C, Currie G. Health economic evaluation. journal of epidemiology and community health. 2002;56:85-8.
10. Higgins JPe, Green Se. Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0): The Cochrane Collaboration; 2011.
11. Brazier J, Ratcliffe J, Salomon JA, Tsuchiya A. Measuring and Valuing Health Benefits for Economic Evaluation. Second edition. Oxford, UK: Oxford University Press; 2017.
12. Woods B, Manca A, Weatherly H, Saramago P, Sideris E, Giannopoulou C, et al. Cost-effectiveness of adjunct non-pharmacological interventions for osteoarthritis of the knee. PLoS One. 2017;12(3):e0172749.
13. Pinto D, Robertson MC, Hansen P, Abbott JH. Cost-effectiveness of nonpharmacologic, nonsurgical interventions for hip and/or knee osteoarthritis: systematic review. Value Health. 2012;15(1):1-12.
14. Felson DT. Osteoarthritis as a disease of mechanics. Osteoarthritis Cartilage. 2013;21(1):10-5.
15. PROSPERO 2015:CRD42015024441 , available at ww.crd.york.ac.uk/PROSPERO. 15 July 2015.
16. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4(1):1-.
17. Organisation WH. ICF. International Classification of Functioning, Disability and Health. 2001. p. 124.
18. Drummond M, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ. 1996;313:275-83.
19. Collaboration TC. Economics Methods Policy Brief 2008.
20. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
21. McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, et al. Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis. Health Technology Assessment. 2004;8(46):iii.
22. Richardson G, Hawkins N, McCarthy CJ, Mills PM, Pullen R, Roberts C, et al. Cost-effectiveness of a supplementary class-based exercise program in the treatment of knee osteoarthritis. International Journal of Technology Assessment in Health Care. 2006;22(1):84-9.
23. Barton GR, Sach TH, Jenkinson C, Doherty M, Avery AJ, Muir KR. Lifestyle interventions for knee pain in overweight and obese adults aged >45: Economic evaluation of randomised controlled trial. BMJ (Online). 2009;339(7721):610-2.

24. Bennell KL, Ahamed Y, Jull G, Bryant C, Hunt MA, Forbes AB, et al. Physical Therapist-Delivered Pain Coping Skills Training and Exercise for Knee Osteoarthritis: Randomized Controlled Trial. Arthritis Care and Research. 2016;68(5):590-602.
25. Cochrane T, Davey RC, Matthes Edwards SM. Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis. Health Technology Assessment (Winchester, England). 2005;9(31):iii.
26. Coupé VMH, Veenhof C, van Tulder MW, Dekker J, Bijlsma JWJ, Van den Ende CHM. The cost effectiveness of behavioural graded activity in patients with osteoarthritis of hip and/or knee. Annals Of The Rheumatic Diseases. 2007;66(2):215-21.
27. Hurley MV, Walsh NE, Mitchell H, Nicholas J, Patel A. Long-term outcomes and costs of an integrated rehabilitation program for chronic knee pain: a pragmatic, cluster randomized, controlled trial. Arthritis Care & Research. 2012;64(2):238-47.
28. Hurley MV, Walsh NE, Mitchell HL, Pimm TJ, Williamson E, Jones RH, et al. Economic evaluation of a rehabilitation program integrating exercise, self-management, and active coping strategies for chronic knee pain. Arthritis And Rheumatism. 2007;57(7):1220-9.
29. Jessep SA, Walsh NE, Ratcliffe J, Hurley MV. Long-term clinical benefits and costs of an integrated rehabilitation programme compared with outpatient physiotherapy for chronic knee pain. Physiotherapy. 2009;95(2):94-102.
30. Juhakoski R, Tenhonen S, Malmivaara A, Kiviniemi V, Anttonen T, Arokoski JP. A pragmatic randomized controlled study of the effectiveness and cost consequences of exercise therapy in hip osteoarthritis. Clinical rehabilitation. 2011;25(4):370-83.
31. Lord J, Victor C, Littlejohns P, Ross FM, Axford JS. Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee. Health Technol Assess. 1999;3(23):1-55.
32. Losina E, Dervan EE, Paltiel AD, Dong Y, Wright RJ, Spindler KP, et al. Defining the value of future research to identify the preferred treatment of meniscal tear in the presence of knee osteoarthritis. PLoS ONE. 2015;10(6).
33. Marra CA, Grubisic M, Cibere J, Grindrod KA, Woolcott JC, Gastonguay L, et al. Cost-utility analysis of a multidisciplinary strategy to manage osteoarthritis of the knee: economic evaluation of a cluster randomized controlled trial study. Arthritis Care & Research. 2014;66(6):810-6.
34. Mazzuca SA, Brandt KD, Katz BP, Hanna MP, Melfi CA. Reduced utilization and cost of primary care clinic visits resulting from self-care education for patients with osteoarthritis of the knee. Arthritis And Rheumatism. 1999;42(6):1267-73.
35. Patel A, Buszewicz M, Beecham J, Griffin M, Rait G, Nazareth I, et al. Economic evaluation of arthritis self management in primary care. BMJ (Clinical Research Ed). 2009;339:b3532-b.

36. Pinto D, Robertson MC, Abbott JH, Hansen P, Campbell AJ. Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee. 2: economic evaluation alongside a randomized controlled trial. Osteoarthritis And Cartilage / OARS, Osteoarthritis Research Society. 2013;21(10):1504-13.
37. Reinhold T, Witt CM, Jena S, Brinkhaus B, Willich SN. Quality of life and cost-effectiveness of acupuncture treatment in patients with osteoarthritis pain. The European Journal Of Health Economics: HEPAC: Health Economics In Prevention And Care. 2008;9(3):209-19.
38. Rome K, Gray J, Stewart F, Hannant SC, Callaghan D, Hubble J. Evaluating the clinical effectiveness and cost-effectiveness of foot orthoses in the treatment of plantar heel pain: a feasibility study. Journal of the American Podiatric Medical Association. 2004;94(3):229-38.
39. Sevick MA, Bradham DD, Muender M, Chen GJ, Enarson C, Dailey M, et al. Cost-effectiveness of aerobic and resistance exercise in seniors with knee osteoarthritis. Medicine & Science in Sports & Exercise. 2000;32(9):1534-40.
40. Stan G, Orban H, Orban C. Cost Effectiveness Analysis of Knee Osteoarthritis Treatment. Chirurgia (Bucur). 2015;110(4):368-74.
41. Tan SS, Teirlinck CH, Dekker J, Goossens LMA, Bohnen AM, Verhaar JAN, et al. Cost-utility of exercise therapy in patients with hip osteoarthritis in primary care. Osteoarthritis and Cartilage. 2016;24(4):581-8.
42. Thomas KS, Miller P, Doherty M, Muir KR, Jones AC, O'Reilly SC. Cost effectiveness of a two-year home exercise program for the treatment of knee pain. Arthritis And Rheumatism. 2005;53(3):388-94.
43. Torkki M, Malmivaara A, Reivonen N, Seitsalo S, Laippala P, Hoikka V. Individually fitted sports shoes for overuse injuries among newspaper carriers. Scandinavian Journal of Work, Environment and Health. 2002;28(3):176-83.
44. Whitehurst DGT, Bryan S, Hay EM, Thomas E, Young J, Foster NE. Cost-Effectiveness of Acupuncture Care as an Adjunct to Exercise-Based Physical Therapy for Osteoarthritis of the Knee. Physical Therapy. 2011;91(5):630-41.
45. Witt CM, Brinkhaus B, Reinhold T, Willich SN. Efficacy, effectiveness, safety and costs of acupuncture for chronic pain - Results of a large research initiative. Acupuncture in Medicine. 2006;24(SUPPL.):S33-S9.
46. Ciani O, Pascarelli NA, Giannitti C, Galeazzi M, Meregaglia M, Fattore G, et al. Mud-Bath Therapy in Addition to Usual Care in Bilateral Knee Osteoarthritis: An Economic Evaluation Alongside a Randomized Controlled Trial. Arthritis Care Res (Hoboken). 2017;69(7):966-72.
47. Sevick MA, Miller GD, Loeser RF, Williamson JD, Messier SP. Cost-effectiveness of exercise and diet in overweight and obese adults with knee osteoarthritis. Med Sci Sports Exerc. 2009;41(6):1167-74.

48. Abbott JH, Robertson MC, Chapple C, Pinto D, Wright AA, Leon de la Barra S, et al. Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: a randomized controlled trial. 1: clinical effectiveness. Osteoarthritis Cartilage. 2013;21(4):525-34.
49. Buszewicz M, Rait G, Griffin M, Nazareth I, Patel A, Atkinson A, et al. Self management of arthritis in primary care: randomised controlled trial. BMJ. 2006;333(7574):879.
50. Cadbury H. Self-care in osteoarthritis. Community nurse. 1997;3(10):28-31.
51. Ettinger WHJ, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, et al. A Randomized Trial Comparing Aerobic Exercise and Resistance Exercise With a Health Education Program in Older Adults With Knee Osteoarthritis: The Fitness Arthritis and Seniors Trial (FAST). Journal of the American Medical Association. 1997;277(1):25-31.
52. Foster NE, Thomas E, Barlas P, Hill JC, Young J, Mason E, et al. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. BMJ. 2007;335(7617):436.
53. Hurley MV, Walsh NE, Mitchell HL, Pimm TJ, Patel A, Williamson E, et al. Clinical effectiveness of a rehabilitation program integrating exercise, self-management, and active coping strategies for chronic knee pain: a cluster randomized trial. Arthritis Rheum. 2007;57(7):1211-9.
54. Jenkinson CM, Doherty M, Avery AJ, Read A, Taylor MA, Sach TH, et al. Effects of dietary intervention and quadriceps strengthening exercises on pain and function in overweight people with knee pain: randomised controlled trial. BMJ. 2009;339:b3170.
55. Katz JN, Brophy RH, Chaisson CE, de Chaves L, Cole BJ, Dahm DL, et al. Surgery versus physical therapy for a meniscal tear and osteoarthritis. N Engl J Med. 2013;368(18):1675-84.
56. Katz JN, Chaisson CE, Cole B, Guermazi A, Hunter DJ, Jones M, et al. The MeTeOR trial (Meniscal Tear in Osteoarthritis Research): rationale and design features. Contemp Clin Trials. 2012;33(6):1189-96.
57. Marra CA, Cibere J, Grubisic M, Grindrod KA, Gastonguay L, Thomas JM, et al. Pharmacist-initiated intervention trial in osteoarthritis: a multidisciplinary intervention for knee osteoarthritis. Arthritis Care Res (Hoboken). 2012;64(12):1837-45.
58. Mazzuca SA, Brandt KD, Katz BP, Chambers M, Byrd D, Ha'a M. Effects of Self-Care Education on the Health Status of Inner-City Patients with Osteoarthritis of the Knee. Arthritis & Rheumatism. 1997;40(8):1466-74.
59. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum. 2004;50(5):1501-10.
60. Thomas KS, Muir KR, Doherty M, Jones AC, O'Reilly SC, Bassey EJ, et al. Home based exercise programme for knee pain and knee

osteoarthritis: randomised controlled trial. BMJ. 2002;325(5 October 2002).
61. Veenhof C, Koke AJ, Dekker J, Oostendorp RA, Bijlsma JW, van Tulder MW, et al. Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: A randomized clinical trial. Arthritis Rheum. 2006;55(6):925-34.
62. Witt CM, Jena S, Brinkhaus B, Liecker B, Wegscheider K, Willich SN. Acupuncture in patients with osteoarthritis of the knee or hip: a randomized, controlled trial with an additional nonrandomized arm. Arthritis Rheum. 2006;54(11):3485-93.
63. Witt C, Brinkhaus B, Jena S, Linde K, Streng A, Wagenpfeil S, et al. Acupuncture in patients with osteoarthritis of the knee: a randomised trial. The Lancet. 2005;366(9480):136-43.
64. Fioravanti A, Bacaro G, Giannitti C, Tenti S, Cheleschi S, Gui Delli GM, et al. One-year follow-up of mud-bath therapy in patients with bilateral knee osteoarthritis: a randomized, single-blind controlled trial. Int J Biometeorol. 2015;59(9):1333-43.
65. Rome K, Gray J, Stewart F, Hannant SC, Callaghan D, Hubble J. Evaluating the Clinical Effectiveness and Cost-effectiveness of Foot Orthoses in the Treatment of Plantar Heel Pain. A Feasibility Study. Journal of the American Podiatric Medical Association. 2004;94(3):229-38.
66. Sevick MA, Miller GD, Loeser RF, Williamson JD, Messier SP. Cost-effectiveness of exercise and diet in overweight and obese adults with knee osteoarthritis. Medicine & Science in Sports & Exercise. 2009;41(6):1167-74.
67. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1323-30.
68. Johnsen LG, Hellum C, Nygaard ØP, Storheim K, Brox JI, Rossvoll I, et al. Comparison of the SF6D, the EQ5D, and the oswestry disability index in patients with chronic low back pain and degenerative disc disease. BMC Musculoskeletal Disorders. 2013;14(148).
69. Devlin N, Brazier J, Pickard AS, Stolk E. 3L, 5L, What the L? A NICE Conundrum. Pharmacoeconomics. 2018.
70. NICE. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. Position statement on use of the EQ-5D-5L valuation set. 2017.
71. Menz HB, Jordan KP, Roddy E, Croft PR. Characteristics of primary care consultations for musculoskeletal foot and ankle problems in the UK. Rheumatology (Oxford, England). 2010;49(7):1391-8.
72. Thomas MJ, Roddy E, Zhang W, Menz HB, Hannan MT, Peat GM. The population prevalence of foot and ankle pain in middle and old age: a systematic review. Pain. 2011;152(12):2870-80.

73. Hill CL, Gill TK, Menz HB, Taylor AW. Prevalence and correlates of foot pain in a population-based study: the North West Adelaide health study. Journal of foot and ankle research. 2008;1(1):2-.
74. Agyekum EK, Ma K. Heel pain: A systematic review. Chinese journal of traumatology = Zhonghua chuang shang za zhi. 2015;18(3):164-9.
75. Woitzik E, Jacobs C, Wong JJ, Cote P, Shearer HM, Randhawa K, et al. The effectiveness of exercise on recovery and clinical outcomes of soft tissue injuries of the leg, ankle, and foot: A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Man Ther. 2015;20(5):633-45.

Figure 1: PRISMA diagram for Systematic review

Table 1: Systematic review study criteria

Criteria	Description
Study design	Included studies were economic evaluation articles with their associated clinical article or studies reporting embedded economic evaluations, of conservative, non-pharmacological and non-surgical interventions for lower extremity musculoskeletal conditions. Excluded studies reported surgical or pharmacological interventions for upper extremity musculoskeletal conditions.
Study participants	Adult humans (as defined by study). Included: Lower extremity (hip, thigh, knee, calf, ankle, foot and toes(s)) musculoskeletal conditions that originate in, and having a mechanical aetiology, affect the musculoskeletal system. Excluded: systemic conditions (such as cancer, vascular, multiple sclerosis, gout, diabetes, for example)
Study time frame	No restrictions
Outcomes measures	Studies were assessed for: Scope and range of evidence of clinical effectiveness and cost effectiveness. Quality of the evidence. Identification of common outcome measures used, clinical and/or economic.
Analysis	Descriptive synthesis, summary of findings table, decision matrix linking clinical effectiveness with cost.

Table 2: Studies included in the review

Main Author+Year	MSK condition	economic evaluation approach (UK definitions)	intervention (number of participants)	comparator (number of participants)	clinical tool (primary outcome)	clinical tool change	economic outcome tool - Quality of Life	Health Related Quality of Life (economic) tool change
Barton, G. R., et al. (2009) (19) [clinical (50)]	knee pain	CUA	dietary intervention plus strengthening exercises (n=109)	leaflet provision (equivalent to standard care) (n=76)	WOMAC	⇧	EQ-5D-3L	⇧
			dietary intervention (n=122)	leaflet provision (equivalent to standard care) (n=76)	WOMAC	⇧	EQ-5D-3L	⇧
			strengthening exercises (n=82)	leaflet provision (equivalent to standard care) (n=76)	WOMAC	⇧	EQ-5D-3L	⇔
Bennell, K.L. et al (2016) (20) [clinical not yet available]	knee OA	CUA	PCST and exercise (n=73)	exercise (n=75)	VAS knee pain plus WOMAC	⇧	AQoL-6D	⇧
			PCST and exercise (n=73)	PCST (n=74)	VAS knee pain plus WOMAC	⇧	AQoL-6D	⇧
			PCST (n=74)	exercise (=75)	VAS knee pain plus WOMAC	⇔	AQoL-6D	⇔
Ciani, O., et al. (2017) (42) [clinical (60)]	knee OA	CUA	Mud-bath therapy (n=53)	usual care (n=50)	WOMAC	⇧	EQ-5D-3L	⇧
Cochrane, T., et al. (2005) (21)	hip OA + knee OA	CUA	water-based exercise (n=153)	usual care (n=159)	WOMAC	⇧	SF36, EQ-5D-3L	
Coupé, V. M. H., et al. (2007) (22) [clinical (57)]	hip OA + knee OA	CUA	Behavioural graded activity (n=56)	usual care (n=66)	VAS knee pain plus WOMAC	⇧	EQ-5D-3L	⇔
Hurley, M. V., et al. (2007) (24) [clinical (49)]	knee pain	CUA	exercise-based rehabilitation program (n=278)	usual care (n=140)	WOMAC	⇧	EQ-5D-3L	⇔

			individual exercise-based rehabilitation program (n=146)	usual care (n=140)	WOMAC	⇔	EQ-5D-3L	⇔
			group exercise-based rehabilitation program (n=132)	usual care (n=140)	WOMAC	⇔	EQ-5D-3L	⇔
			group exercise-based rehabilitation program (n=132)	Individual exercise-based rehabilitation program (n=146)	WOMAC	⇔	EQ-5D-3L	⇔
Hurley, M. V., et al. (2012) (23)	knee pain	CUA	exercise-based rehabilitation program (n=189)	usual care (n=94)	WOMAC	⇔	*as clinical*	--
Jessep, S. A., et al. (2009) (25)	knee OA	CEA	exercise-based rehabilitation program (n=29)	outpatient physiotherapy (n=35)	WOMAC	⇔	EQ-5D-3L	⇔
Juhakoski, R., et al. (2011) (26)	hip OA	CCA	combined exercise and usual care (n=60)	usual care (n=58)	WOMAC	⇔	RAND-36 (SF-36)	⇔
Lord, J., et al. (1999) (27) [clinical (46)]	knee OA	CMA	Nurse-led education (n=105)	usual care (n=65)	WOMAC	⇔	SF-36	⇔
Losina, E., et al. (2015) (28) [clinical (51, 52)]	knee OA	CUA	arthroscopic partial meniscectomy (n=351)	physical therapy (n=164)	WOMAC	⇔	EQ-5D-3L	--
Marra, C. A., et al. (2014) (29) [clinical	knee OA	CUA	Pharmacist led health care (n=66)	usual care (n=73)	Arthritis Foundation quality indicators for the management of OA	⇔	HUI3	⇔
Mazzuca, S. A., et al. (1999) (30) [clinical (54)]	knee OA	CCA	education (individualized arthritis self-care instruction) (n=105)	attention control (n=106)	HAQ	⇔	n/a (health care utilisation and costs data)	--
McCarthy, C. J., et al. (2004) (17)	knee OA	CUA	class-based exercise programme + home	home exercise programme (n=103)	timed measure of locomotor	⇔	EQ-5D-3L	⇔

			exercise programme (n=111)					
Patel, A., et al. (2009) (31) [clinical (45)]	hip OA + knee OA	CUA	Arthritis self management programme plus an education booklet (n=406)	education booklet (reflects standard care) (n=406)	SF-36	⇔	EQ-5D-3L	⇔
Pinto, D., et al. (2013) (32) [clinical (44)]	hip OA + knee OA	CUA	manual therapy (n=54)	usual care (n=51)	WOMAC	⇧	SF12v2 (SF-6D)	⇧
			exercise therapy (n=51)	usual care (n=51)	WOMAC	⇧	SF12v2 (SF-6D)	⇧
			manual and exercise therapy (n=50)	usual care (n=51)	WOMAC	⇧	SF12v2 (SF-6D)	⇧
Reinhold, T., et al. (2008) (33) [clinical (58)]	OA	CUA	acupuncture (n=246)	delayed acupuncture (equivalent to no treatment) (n=243)	WOMAC	⇧	SF-36 (SF-6D)	⇧
Richardson, G., et al. (2006) (18)	knee OA	--	--	--	--	--	--	--
Rome, K., et al. (2004) (61)	heel pain	CUA	accomodative orthoses (n=22)	functional orthoses (n=26)	FHSQ	⇧	EQ-5D-3L	⇧
Sevick, M. A., et al. (2000) (35) [clinical (47)]	knee OA	CEA	aerobic exercise (n=144)	education booklet (reflects standard care) (n=149)	investigator-developed questionnaire	⇧	investigator-developed questionnaire	--
			resistance exercise (n=146)	education booklet (reflects standard care) (n=149)	investigator-developed questionnaire	⇧	investigator-developed questionnaire	--
			resistance exercise (n=146)	aerobic exercise (n=144)	investigator-developed questionnaire	⇧	investigator-developed questionnaire	--
Sevick, M. A., et al. (2009) (43) [clinical (55)]	knee OA	CEA	diet (n=82)	healthy lifestyle control (attention control comparison) (n=78)	WOMAC	⇧	*as clinical*	--
			exercise (n=80)	healthy lifestyle control (attention control	WOMAC	⇧	*as clinical*	--

				comparison) (n=78)				
			diet + exercise (n=76)	healthy lifestyle control (attention control comparison) (n=78)	WOMAC	⇔	*as clinical*	--
			diet + exercise (n=76)	diet (n=82)	WOMAC	⇔	*as clinical*	--
			diet + exercise (n=76)	exercise (n=80)	WOMAC	⇔	*as clinical*	--
			exercise (n=80)	diet (n=82)	WOMAC	⇔	*as clinical*	--
Stan, G., et al. (2015) (36)	knee OA	CUA	unilateral TKA (non-operated knee) (n=30)	rehabilitation care (n=30)	EQ-5D-3L	⇔	*as clinical*	--
			TKA following HTO (n=30)	rehabilitation care (n=30)	EQ-5D-3L	⇔	*as clinical*	--
			unilateral TKA (non-operated knee) (n=30)	TKA following HTO (n=30)	EQ-5D-3L	⇔	*as clinical*	--
Tan, S.S. et al (2016) (37)	hip OA	CUA	exercise therapy added to GP care (n=101)	GP care (n=102)	HOOS	[forthcoming paper]	EQ-5D-3L	⇔
Thomas, K. S., et al. (2005) (38) [clinical (56)]	knee pain	CEA	exercise + telephone support + placebo (n=114)	exercise + telephone support (n=121)	WOMAC	⇔	*as clinical*	--
			placebo (n=78)	no intervention (=78)	WOMAC	⇔	*as clinical*	--
			exercise therapy (n=235)	Combined no intervention and placebo (n=156)	WOMAC	⇔	*as clinical*	--
			monthly telephone support (n=160)	Combined no intervention and placebo (n=156)	WOMAC	⇔	*as clinical*	--
			exercise + telephone support (combining exercise + telephone support with exercise + telephone support + placebo) (n=235)	Combined no intervention and placebo (n=156)	WOMAC	⇔	*as clinical*	--
Torkki, M., et al. (2002) (39)	overuse injuries	CCA	new, individually adjusted footwear with	subjects' own, used footwear (n=90)	Investigator developed	⇔	*as clinical*	--

			good shock absorbing properties (n=86)		questionnaire			
Whitehurst, D. G. T., et al. (2011) (40) [clinical (48)]	knee OA	CUA	advice and exercise plus true acupuncture (n=117)	advice and exercise (n=116)	WOMAC	⇧	EQ-5D-3L	⇔
			advice and exercise plus true acupuncture (n=117)	advice and exercise plus non-penetrating acupuncture (n=119)	WOMAC	⇔	EQ-5D-3L	⇔
Witt, C. M., et al. (2006) (41) [clinical (58, 59)	chronic pain	CUA	acupuncture (n=322)	usual care (n=210)	WOMAC	⇧	SF-36	⇧

⇧statistically significant change, ⇔not a statistically significant change. Statistical significance based on author's definition. AQoL-6D: Assessment of Quality of Life – 6D scale; EQ5D: EuroQol 5 dimensions; EQ-VAS: EuroQol visual analogue scale; FHSQ: Foot Health Status Questionnaire; HOOS: Hip disability and Osteoarthritis Outcome Score; HUI3: Health Utilities Index Mark 3; SF-6D: Short form 6 Dimensions; SF-12: Short form 12; RAND-36: Finnish-validated SF-36-item Health Survey; SF-36: Short form 36; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; VAS: Visual Analogue Scale.

Table 3: Summary of interventions by lower extremity (26 included studies)

Anatomical location of MSK condition						
Intervention (examples)	lower limbs (general)	hip and knee	hip	knee	foot	total
acupuncture (deep needling, superficial needling, true acupuncture, non-penetrating)		2		1		3
education (education booklet, self-care education, nurse-led education programme)		1		2		3
exercise (aerobic exercise, resistance exercise, exercise aimed at increasing lower limb strength, and endurance, and improving balance)		2	2	7		11
exercise + diet (health eating diet plus quadriceps strengthening exercises)				2		2
exercise + education (behavioural graded activity integrating the concepts of operant conditioning with exercise therapy, supervised exercise and pain management and coping strategies)		1		2		3
footwear (functional orthoses, accommodative orthoses, sports shoe)	1				1	2
mud-bath therapy (mud-packs and hot mineral baths in addition to usual treatment)				1		1
physical therapy (manual physiotherapy)				1		1
Total	1	6	2	16	1	

Table 4: Quality of economic evaluation and clinical reporting in the studies included in the review

	Quality score		
Main Author (Year)	**Economic**	**Clinical (included)**	**Clinical (separate article)**
Barton, G. R., et al. (2009)	85%[a]		14%[c]
Bennell, K. L., et al. (2016)	100%[a]	86%[a]	
Ciani, O., et al. (2017)	92%[a]		71%[a]
Cochrane, T., et al. (2005)	83%[a]	71%[a]	
Coupé, V. M. H., et al. (2007)	92%[a]		86%[a]
Hurley, M. V., et al. (2007)	100%[a]		86%[a]
Hurley, M. V., et al. (2012)	100%[a]	86%[a]	
Jessep, S. A., et al. (2009)	55%[b]	57%[b]	
Juhakoski, R., et al. (2011)	46%[c]	71%[a]	
Lord, J., et al. (1999)	100%[a]		14%[c]
Losina, E., et al. (2015)	87%[a]		71%[a]
Marra, C. A., et al. (2014)	100%[a]		57%[b]
Mazzuca, S. A., et al. (1999)	67%[b]		57%[b]
McCarthy, C. J., et al. (2004)	100%[a]	71%[a]	
Patel, A., et al. (2009)	100%[a]		86%[a]
Pinto, D., et al. (2013)	100%[a]		86%[a]
Reinhold, T., et al. (2008)	77%[a]	43%[c]	
Richardson, G., et al. (2006)[d]	--	--	
Rome, K., et al. (2004)	83%[a]	57%[b]	
Sevick, M. A., et al. (2000)	67%[b]		71%[a]
Sevick, M. A., et al. (2009)	85%[a]		86%[a]
Stan, G., et al. (2015)	31%[c]	0%[c]	
Tan, S. S., et al. (2016)	100%[a]	57%[b]	
Thomas, K. S., et al. (2005)	92%[a]		71%[a]
Torkki, M., et al. (2002)	50%[b]	71%[a]	
Whitehurst, D. G. T., et al. (2011)	100%[a]		71%[a]
Witt, C. M., et al. (2006)	31%[c]		57%[b]

Quality score as % of eligible items: [a]70-100%; [b]50-70%; [c]<50%. [d]see McCarthy, 2004.

Table 5: Matrix of reported clinical and cost effectiveness evidence

			Declining effectiveness		
			→	→	→
			1 (evidence of greater effectiveness)	2 (evidence of no difference in effectiveness)	3 (evidence of less effectiveness)
Increased cost	↓	A (evidence of cost savings)	(21) water-based exercise vs usual care for hip OA and knee OA (24) exercise-based rehabilitation program vs usual care for knee pain (38) Exercise and telephone support vs telephone support for knee pain (42) mud-bath therapy added to standard care vs standard therapy alone		
	↓	B (evidence of no difference in costs)	(24) exercise-based rehabilitation program vs usual care for knee pain (20) pain coping skills training/exercise vs exercise for knee OA (20) pain coping skills training/exercise vs PCST for knee OA	(22) behavioural graded activity vs usual care for hip OA and knee OA (17, 18) class-based exercise programme + home exercise programme vs home exercise programme for knee OA (40) advice and exercise plus true acupuncture vs advice and exercise plus non-penetrating acupuncture for knee OA	

	↓	C (evidence of greater costs)	(32) manual therapy vs usual care for hip OA and knee OA (32) exercise therapy vs usual care for hip OA and knee OA (32) manual and exercise therapy vs usual care for hip OA and knee OA (43) Diet and exercise vs health lifestyle control (40) advice and exercise plus true acupuncture vs advice and exercise for knee OA	(24) Group-based exercise-based rehabilitation program vs individual-based exercise programme for knee pain (31) arthritis self-management programme plus an education booklet vs education booklet (reflects standard care) for hip OA and knee OA (62) Diet vs healthy lifestyle control for knee OA (62) exercise vs healthy lifestyle control for knee OA	(20) pain coping skills training vs exercise for knee OA
	↓	D (not enough evidence on costs)			

Matrix adapted with permissions from hardcopy of Donaldson, C., M. Mugford, and L. Vale, Evidence-based Health Economics: From effectiveness to efficiency in systematic review. 1 ed. 2002: BMJ Books. 168 (8), now available as eBook from Wiley. Evidence of clinical and cost effectiveness reported in studies included in the review with appraised quality score between 70% to 100%.

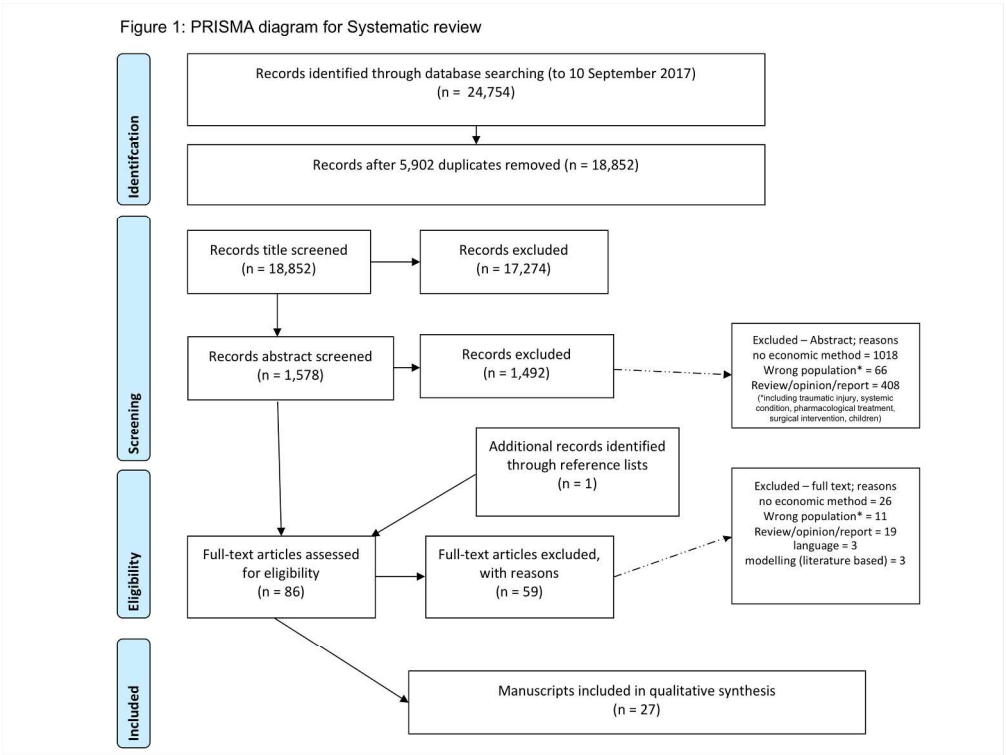

Figure 1: PRISMA diagram for Systematic review

317x238mm (288 x 288 DPI)